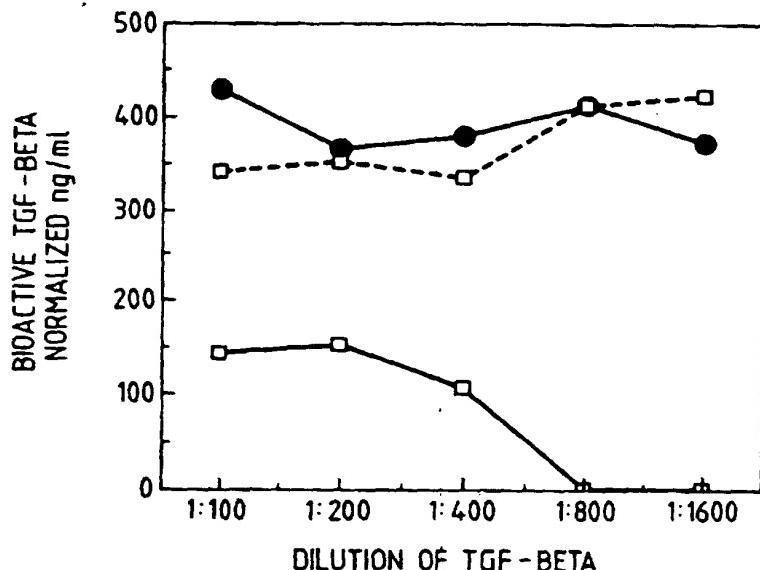




## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>5</sup> : C12N 15/16, 15/12, C12P 21/02 A61K 37/43, G01N 33/74 C12N 1/21, 5/10	A3	(11) International Publication Number: WO 91/08291 (43) International Publication Date: 13 June 1991 (13.06.91)
<p>(21) International Application Number: PCT/US90/06292            (22) International Filing Date: 30 October 1990 (30.10.90)</p> <p>(30) Priority data: 441,680 22 November 1989 (22.11.89) US</p> <p>(71) Applicant: GENENTECH, INC. [US/US]; 460 Point San Bruno Boulevard, South San Francisco, CA 94080 (US).</p> <p>(72) Inventors: LEVINSON, Arthur ; 500 Ramillard Drive, Hillsborough, CA 94010 (US). HAMMONDS, Glenn, R. ; 7036 Norfolk Road, Berkeley, CA 94705 (US). MASON, Anthony ; 1446 Floribunda Avenue, #204, Burlingame, CA 94010 (US).</p>		<p>(74) Agents: HASAK, Janet, E. et al.; Genentech, Inc., 460 Point San Bruno Boulevard, South San Francisco, CA 94080 (US).</p> <p>(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent).</p> <p><b>Published</b>  <i>With international search report.            Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p> <p>(88) Date of publication of the international search report: 12 December 1991 (12.12.91)</p>

(54) Title: LATENCY ASSOCIATED PEPTIDE AND USES THEREFOR



## (57) Abstract

An isolated nucleic acid sequence is provided that comprises a sequence that encodes a latency associated peptide having a molecular weight of about 75,000 when measured by non-reducing SDS-PAGE and capable of antagonizing a biological activity of mature TGF- $\beta$ , provided that the sequence does not also encode a mature TGF- $\beta$ . The latency associated peptide so produced is useful therapeutically in blocking a deleterious activity of an endogenously released or exogenously administered TGF- $\beta$ , alone or in combination with another exogenously administered or endogenously released immune regulator. It is also useful as a co-treatment therapy with mature TGF- $\beta$ , which forms a latent associated complex therewith that is activatable at the desired site *in vivo*.

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DE	Germany	MC	Monaco	US	United States of America
DK	Denmark				

# INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 90/06292

## I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) \*

According to International Patent Classification (IPC) or to both National Classification and IPC C 12 N 15/16,  
 IPC: 5 15/12, C 12 P 21/02, A 61 K 37/43, G 01 N 33/74, C 12 N  
 1/21, 5/10

## II. FIELDS SEARCHED

Minimum Documentation Searched ?

Classification System	Classification Symbols
IPC <sup>5</sup>	C 12 N, C 12 P, C 07 K, A 61 K, G 01 N

Documentation Searched other than Minimum Documentation  
to the Extent that such Documents are Included in the Fields Searched \*

## III. DOCUMENTS CONSIDERED TO BE RELEVANT\*

Category *	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
X	EP, A, 0293785 (ONCOGEN) 7 December 1988, see page 24, line 10 - page 26, line 14; page 28, line 44 - page 31, line 33; page 36, line 15 - page 37, line 50; claim. 14; figures 26,11-13,16-20 --	1-7,9-10,13- 16,19-20,24- 28
X	FEBS Letters, vol. 242, no. 2, January 1989 Elsevier Science Publishers B.V. (Biomedical Division) F. Okada et al.: "One of two subunits of masking protein in latent TGF-beta is a part of pro-TGF-beta" pages 240-244 see the whole article cited in the application --	1-7,9-10, 13-16,19-20, 24-28

\* Special categories of cited documents: <sup>10</sup>

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*U\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

\*W\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*Z\* document member of the same patent family

## IV. CERTIFICATION

Date of the Actual Completion of the International Search

16th July 1991

Date of Mailing of this International Search Report

05.11.91

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

*M. van der Drift*  
Name: M. van der Drift

## III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, ** with indication, where appropriate, of the relevant passages	Relevant to Claim No.
P,X	Science, vol. 247, 16 March 1990, A.M. Gray et al.: "Requirement for activin A and transforming growth factor-beta1 pro-regions in homodimer assembly", pages 1328-1330 see the whole article --	1-7,9-13, 15-16,19-20, 24-28
P,X	EP, A, 0356935 (ONCOGEN LTD PARTNERSHIP) 7 March 1990 see page 4, lines 32-35; page 8, lines 39-45; page 9, lines 15-38; claims --	1-7,9-10,13- 16,19-20, 24-33
P,A	--	14
P,X	EP, A, 0376785 (ONCOGEN LTD PARTNERSHIP) 4 July 1990 see page 25, line 40 - page 26, line 53 --	1-7,9-10,13- 16,19-20,24- 28
A	The Journal of Biological Chemistry, vol. 263, no. 16, 5 June 1988, (US) L.M. Wakefield et al.: "Latent transforming growth factor-beta from human platelets", pages 7646-7654 see the whole article cited in the application --	1
A	EP, A, 0269408 (GENENTECH, INC.) 1 June 1988 see the whole document	29-33,42-44
-----		

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V.  OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE<sup>1</sup>

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1.  Claim numbers ...XXX... because they relate to subject matter not required to be searched by this Authority, namely:

Claims 34-41, 45-50

See PCT Rule 39.1(iv)

Methods for treatment of the human or animal body by means of surgery or therapy, as well as diagnostic methods.

2.  Claim numbers ..... because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3.  Claim numbers..... because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI.  OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING<sup>2</sup>

This International Searching Authority found multiple inventions in this International application as follows:

Claims 1-28, 51

Claims 29-33, 42-44

Please refer to Form PCT/ISA/206 dated 11th March 1991

1.  As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the international application.

2.  As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims of the International application for which fees were paid, specifically claims:

3.  No required additional search fees were timely paid by the applicant. Consequently, this International search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4.  As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- The additional search fees were accompanied by applicant's protest.

- No protest accompanied the payment of additional search fees.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT  
ON INTERNATIONAL PATENT APPLICATION NO.**

**US 9006292**

**SA 42224**

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 13/08/91. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A- 0293785	07-12-88	AU-A-	1673888	01-12-88
		JP-A-	1257497	13-10-89
EP-A- 0356935	07-03-90	JP-A-	2160723	20-06-90
EP-A- 0376785	04-07-90	CA-A-	2005459	16-06-90
EP-A- 0269408	01-06-88	JP-A-	63211234	02-09-88

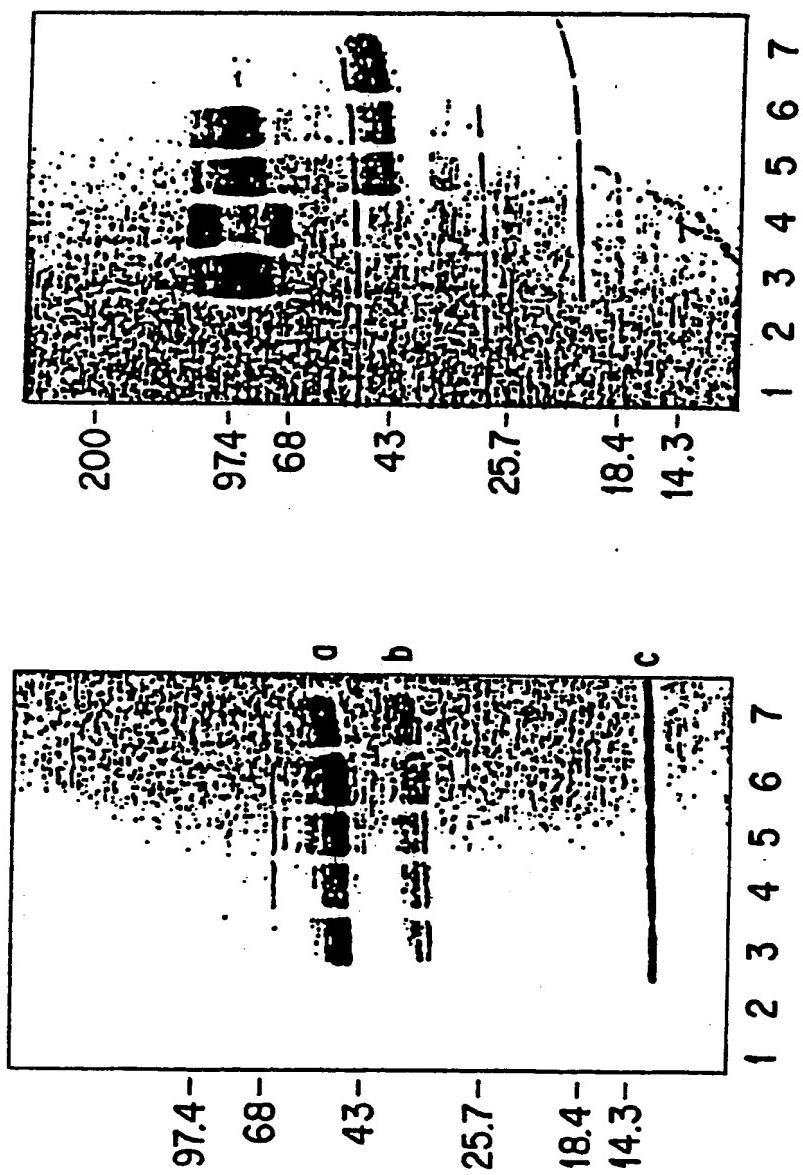
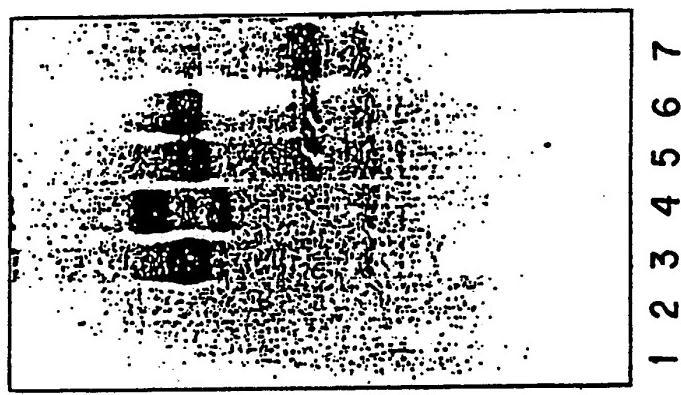
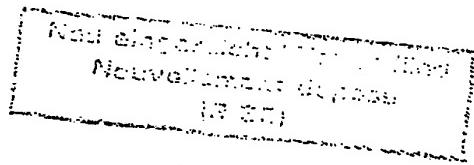


FIG.33D

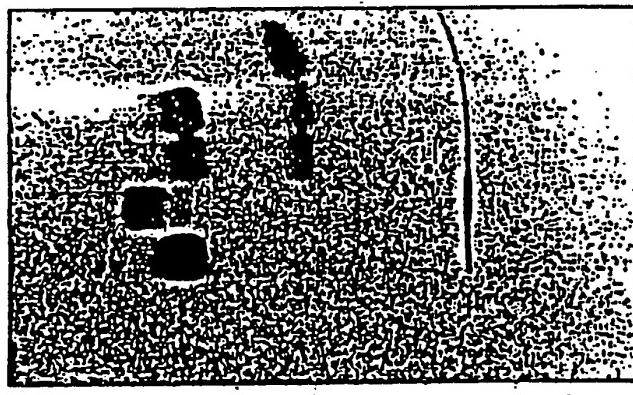
FIG.33E



97.4-  
68-  
43-  
25.7-  
18.4-  
14.3-

1 2 3 4 5 6 7

FIG. 33G



97.4-  
68-  
43-  
25.7-  
18.4-  
14.3-

1 2 3 4 5 6 7

FIG. 33F

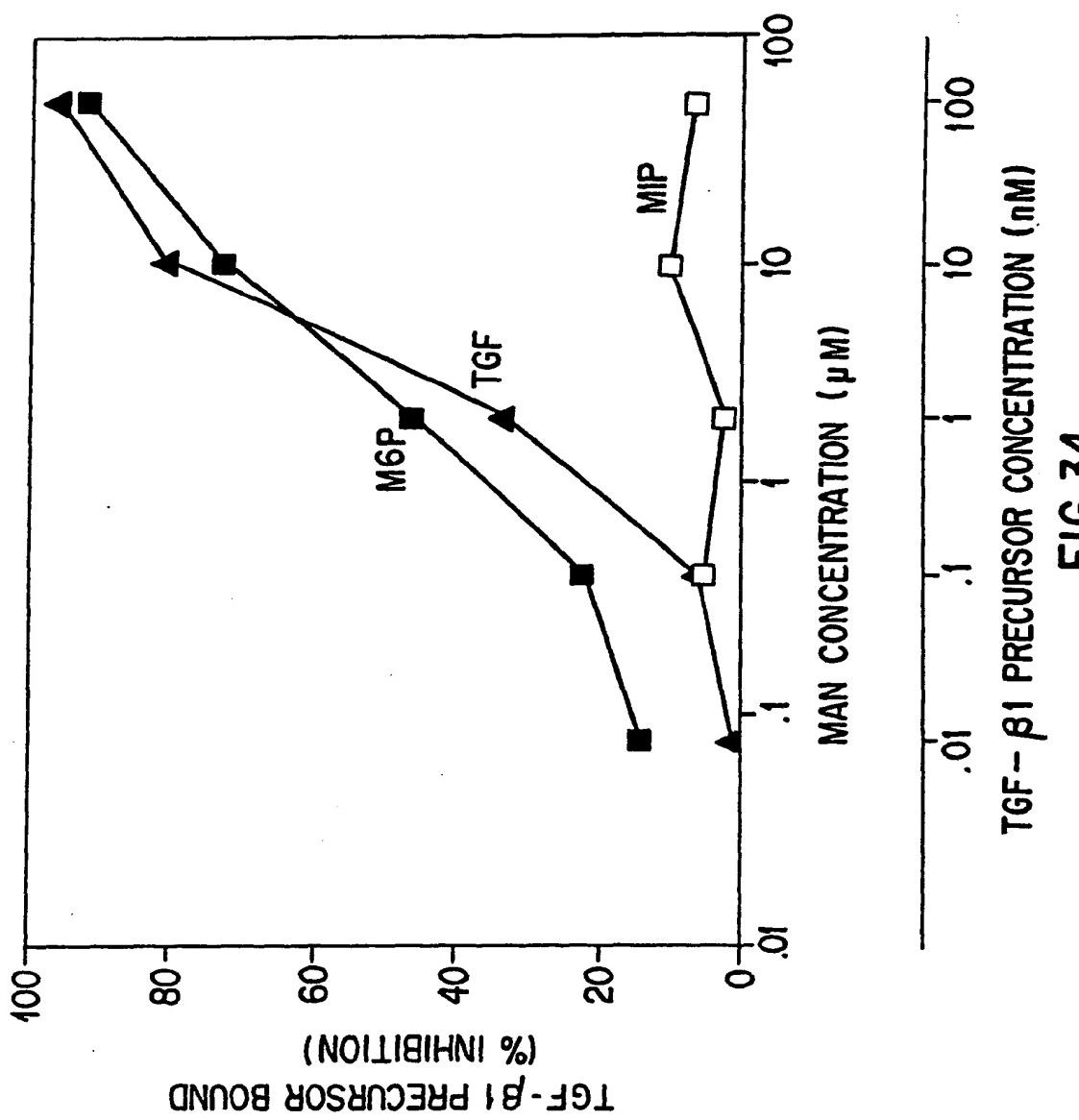


FIG. 34

100,000,000

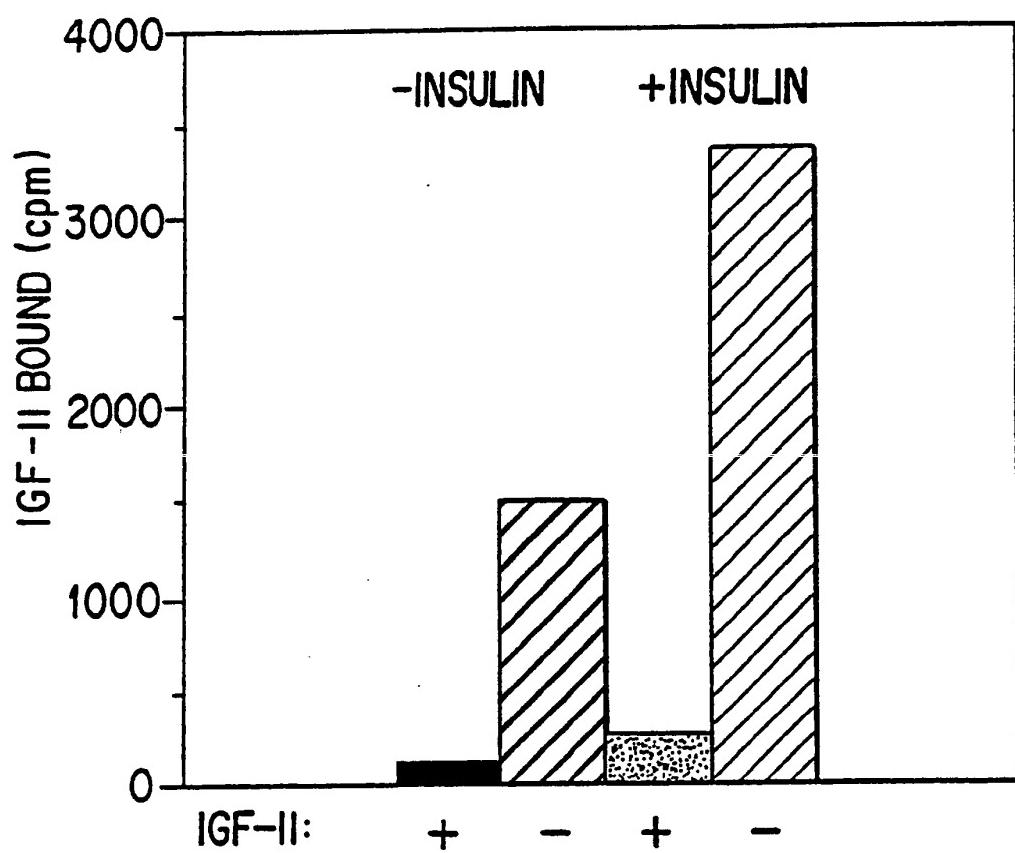


FIG. 35A

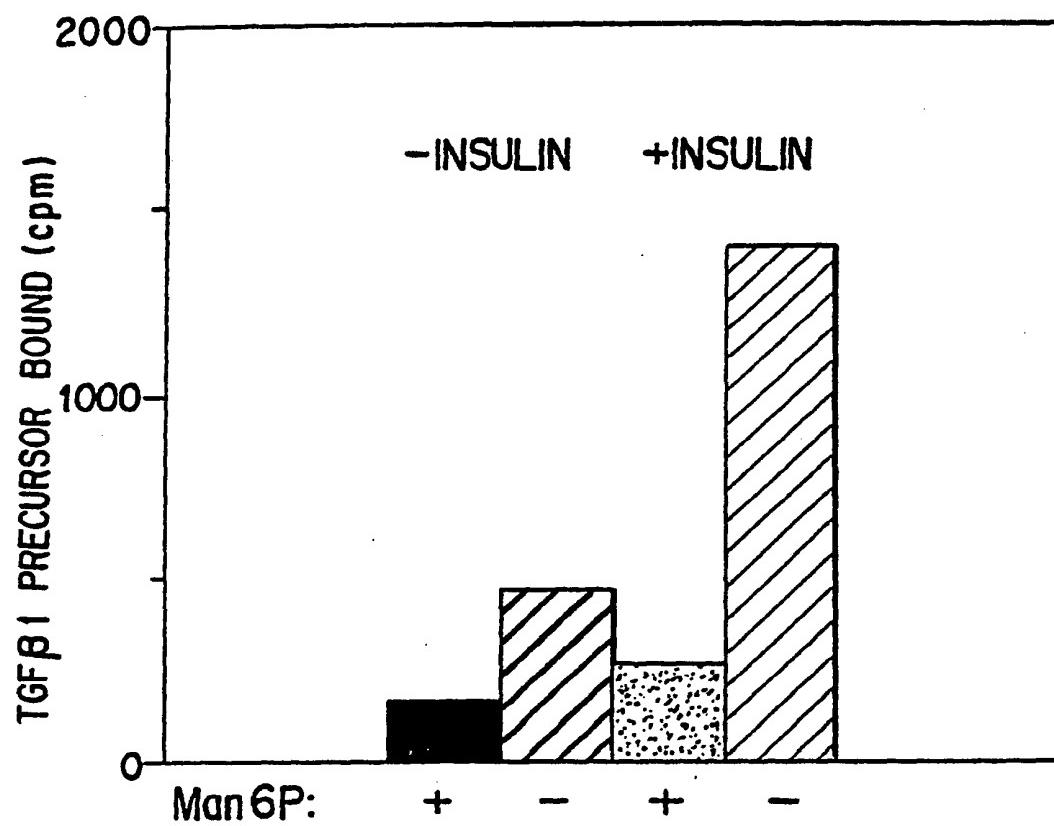


FIG. 35B

10.000.000

Net absorption (cpm) / (cpm binding)

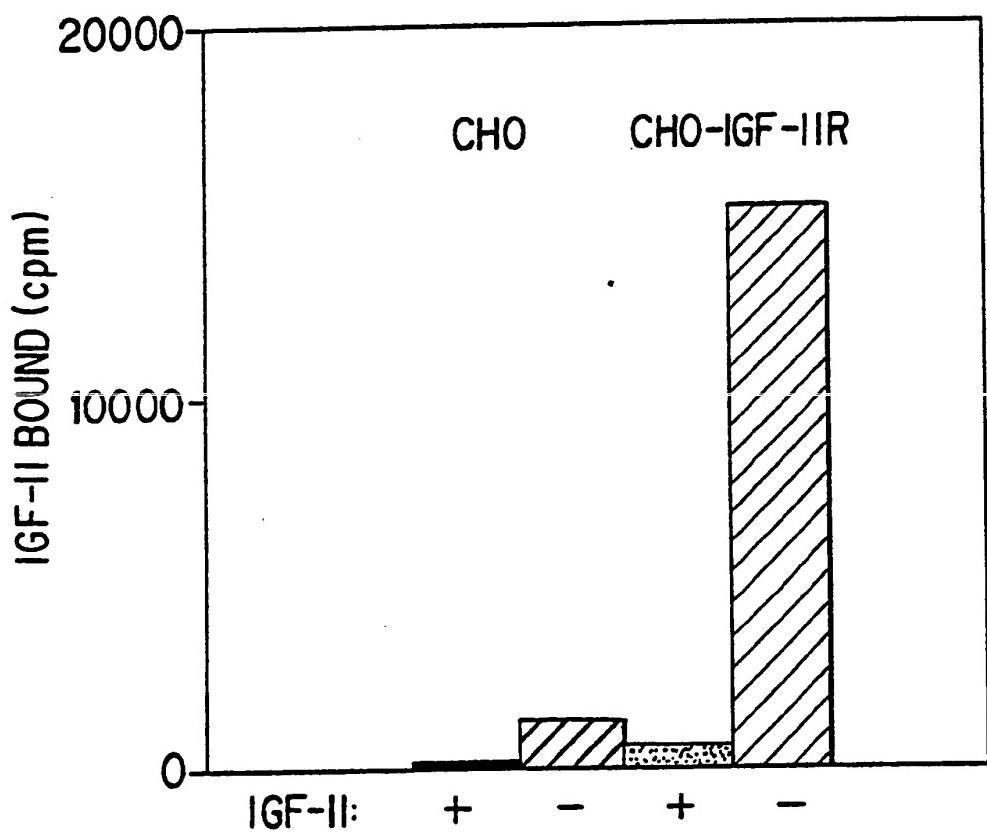


FIG. 36A

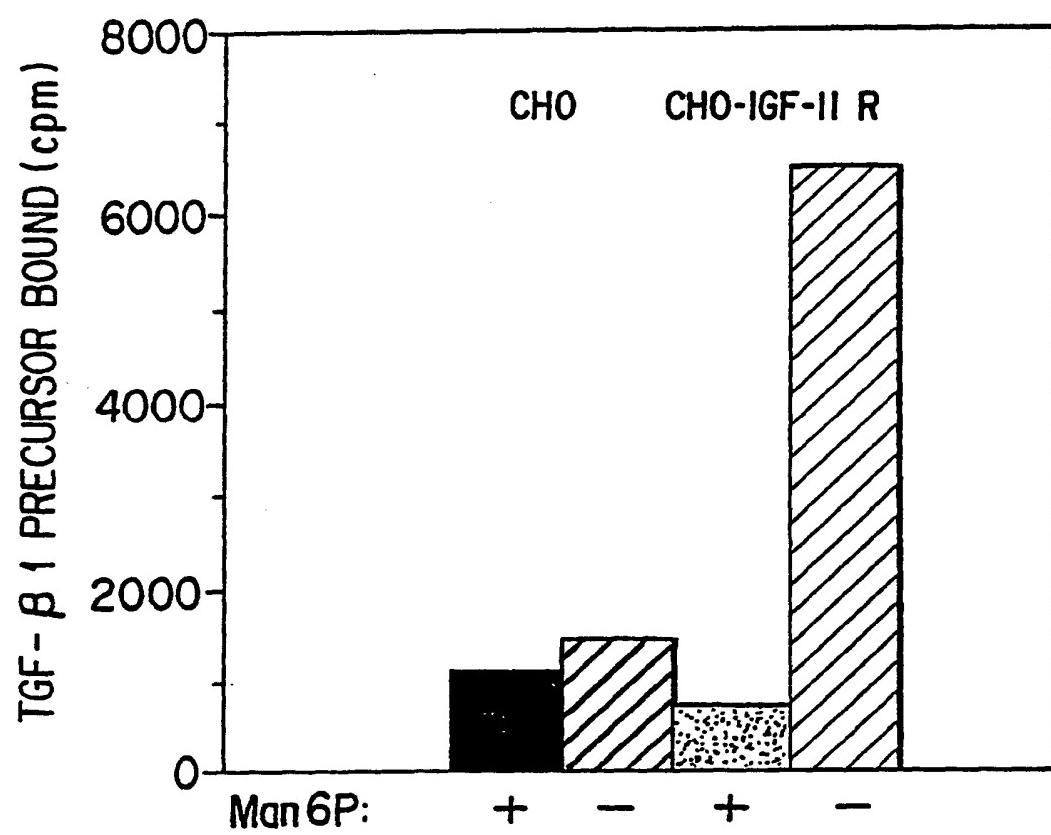


FIG. 36B

Neu et al. (1989) J. Cell. Physiol.  
Nouvellement r. 1989  
(2/89)

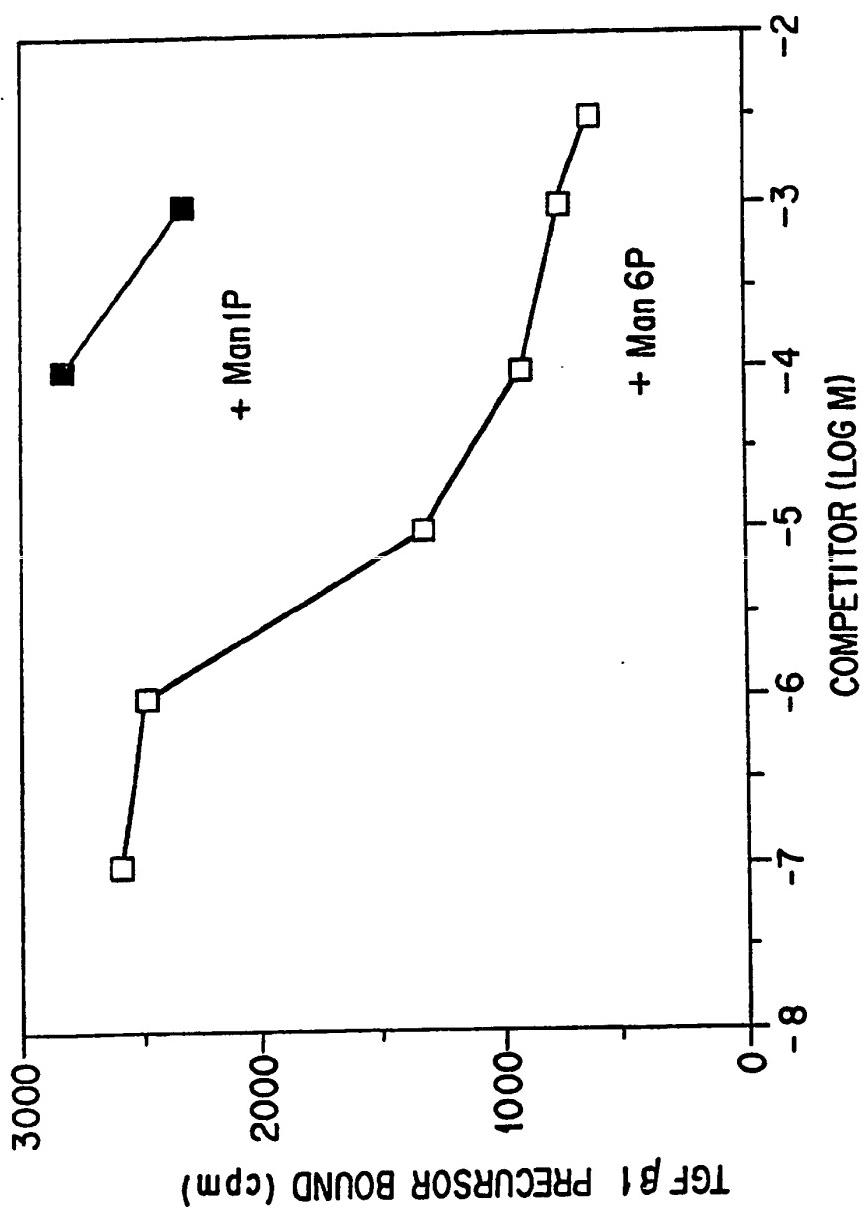


FIG. 37A

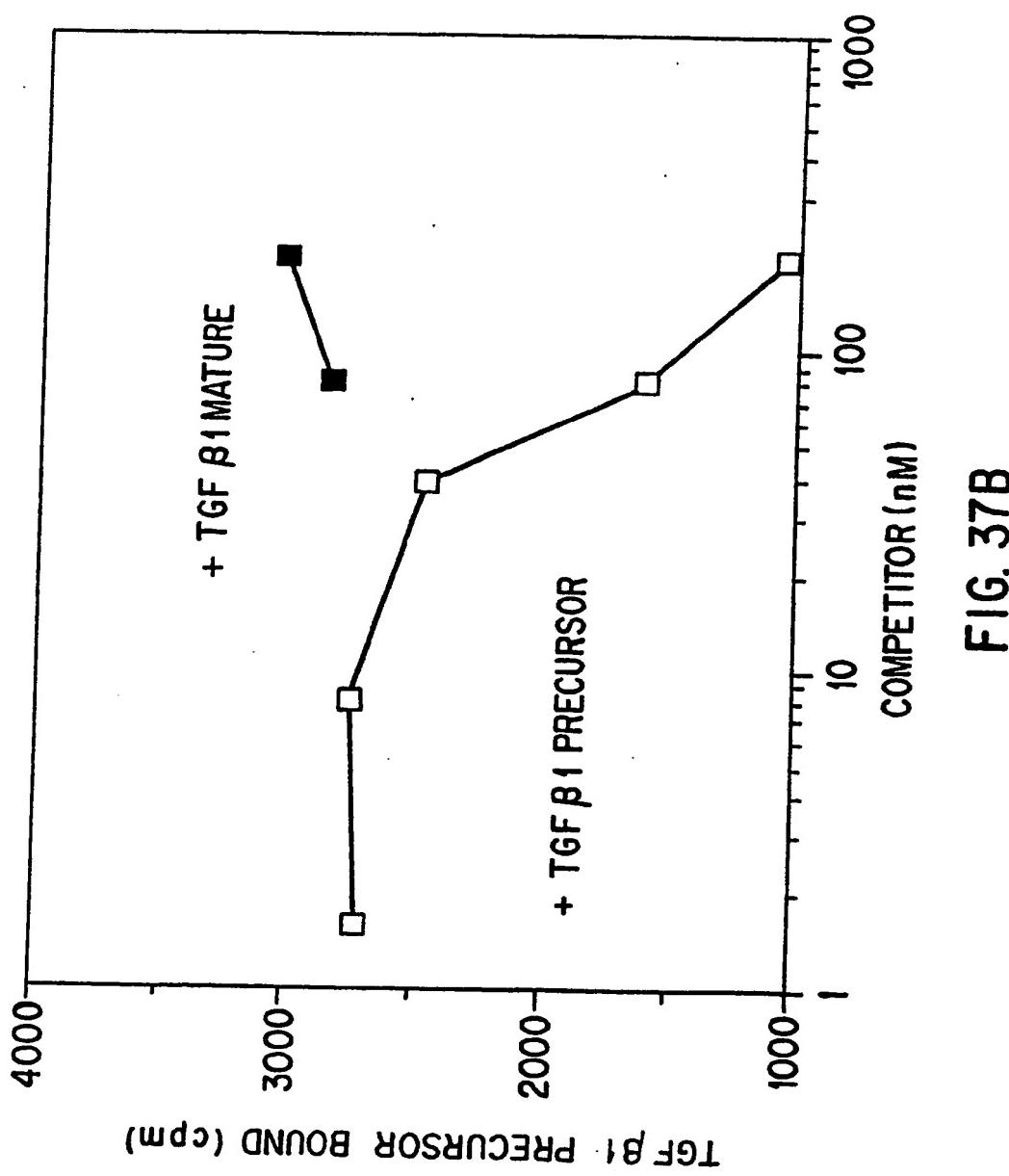


FIG. 37B

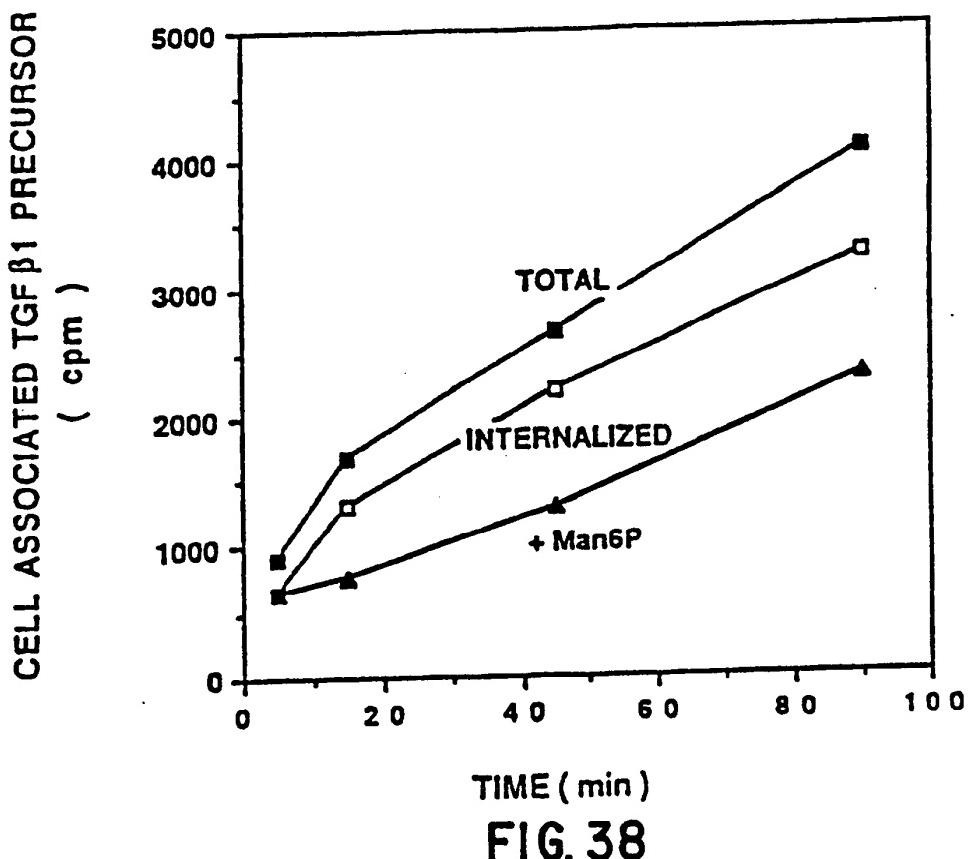


FIG. 38

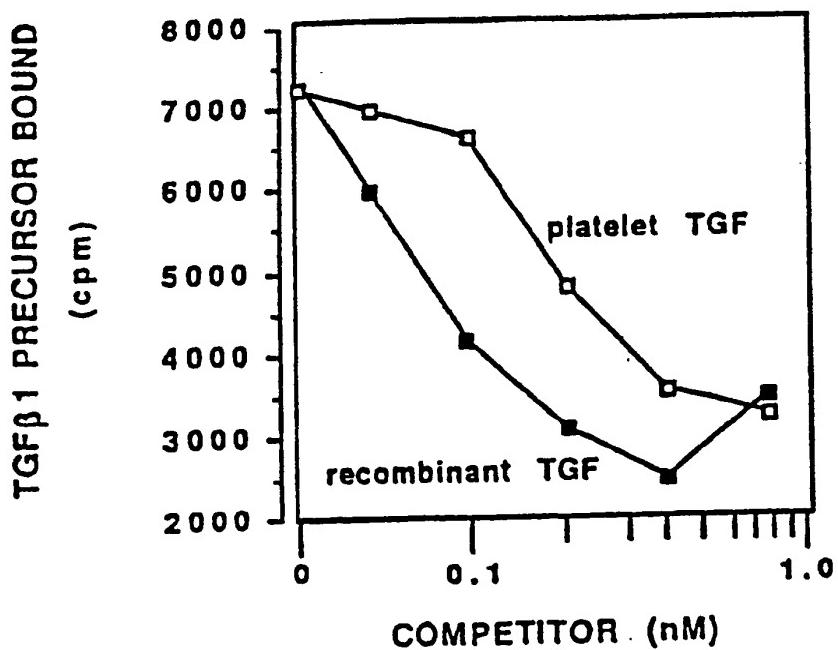


FIG. 39

2.000.000

## BLOTS PROBED WITH:

ANTI-TGF

MAN6P RECEPTOR

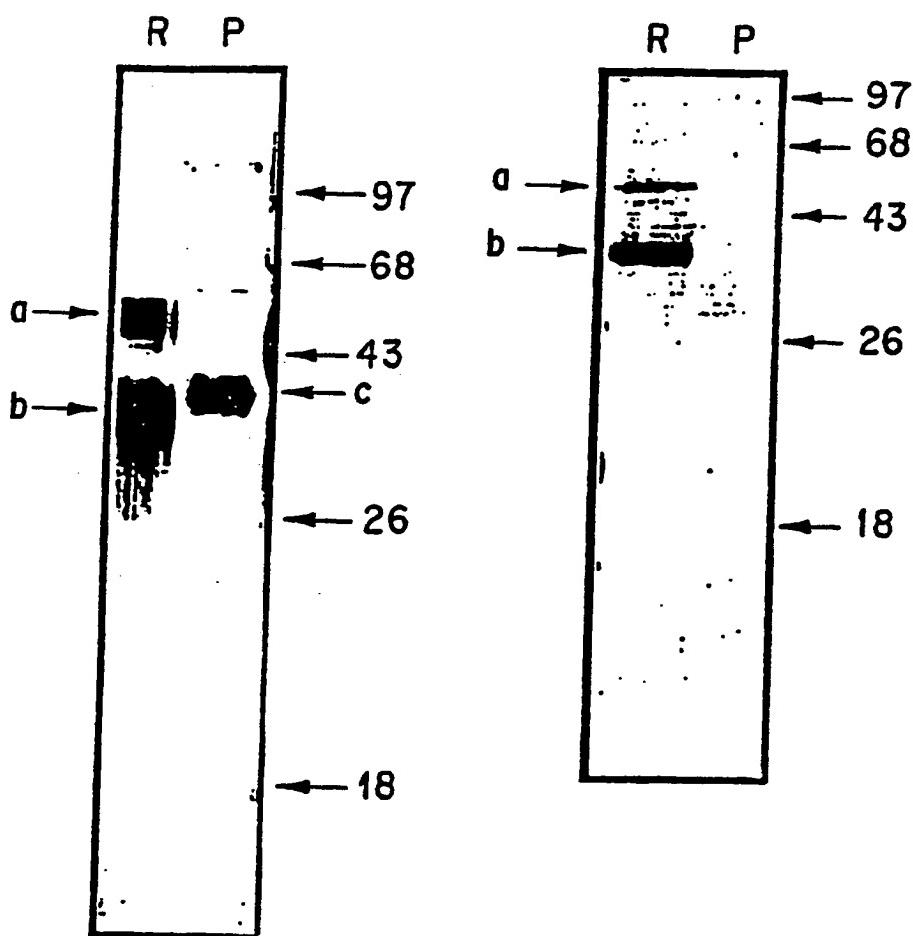


FIG. 40

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INDEXED  
FILED  
RECORDED  
JULY 1980  
FBI - WASH. D.C.

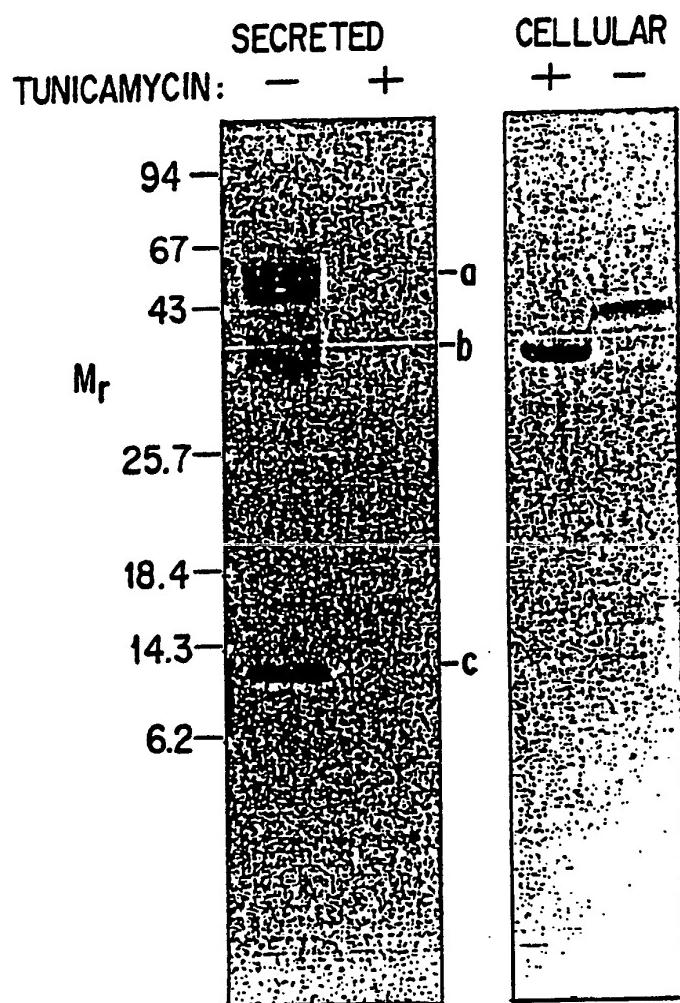


FIG. 41

10.00.90

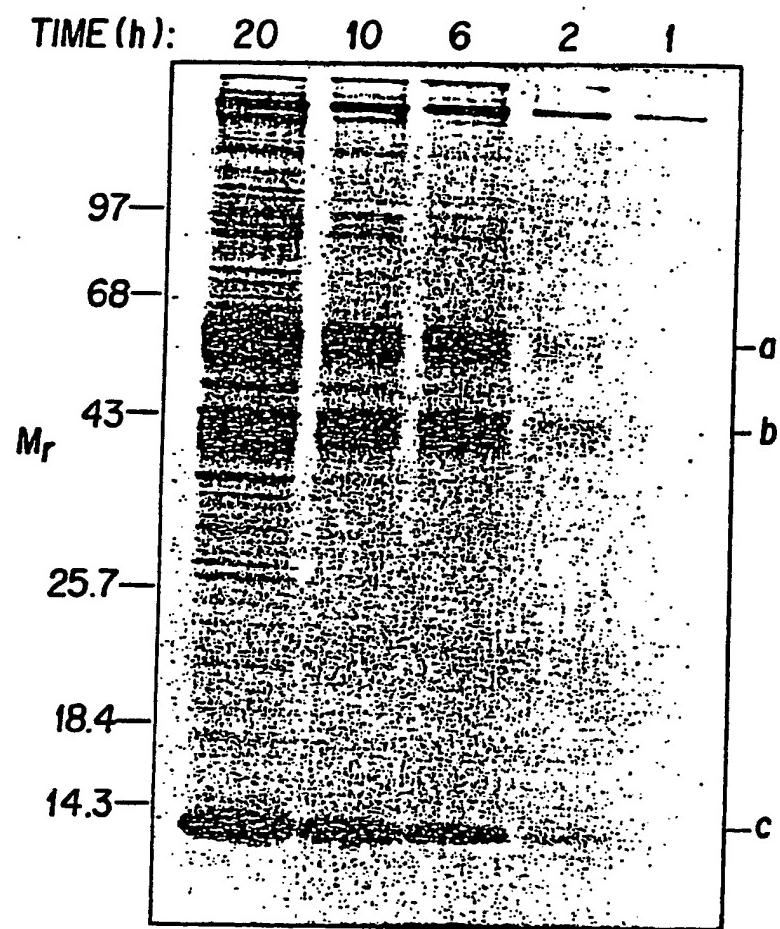


FIG.42A

10.00-00

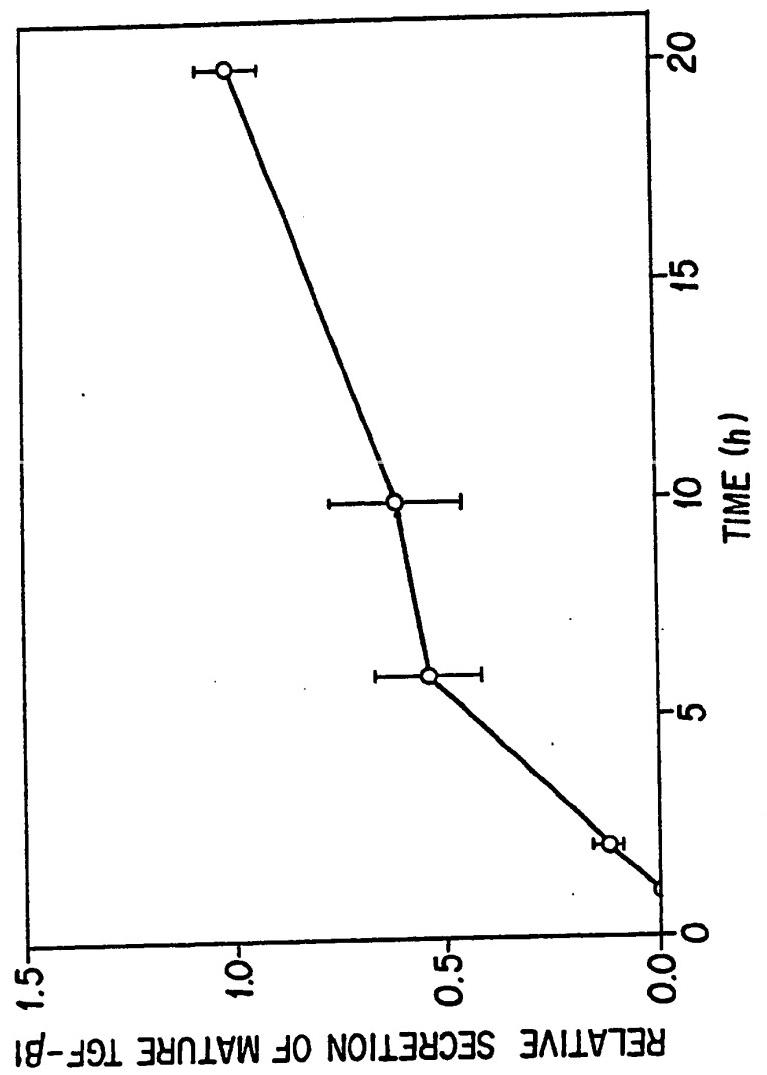


FIG. 42B

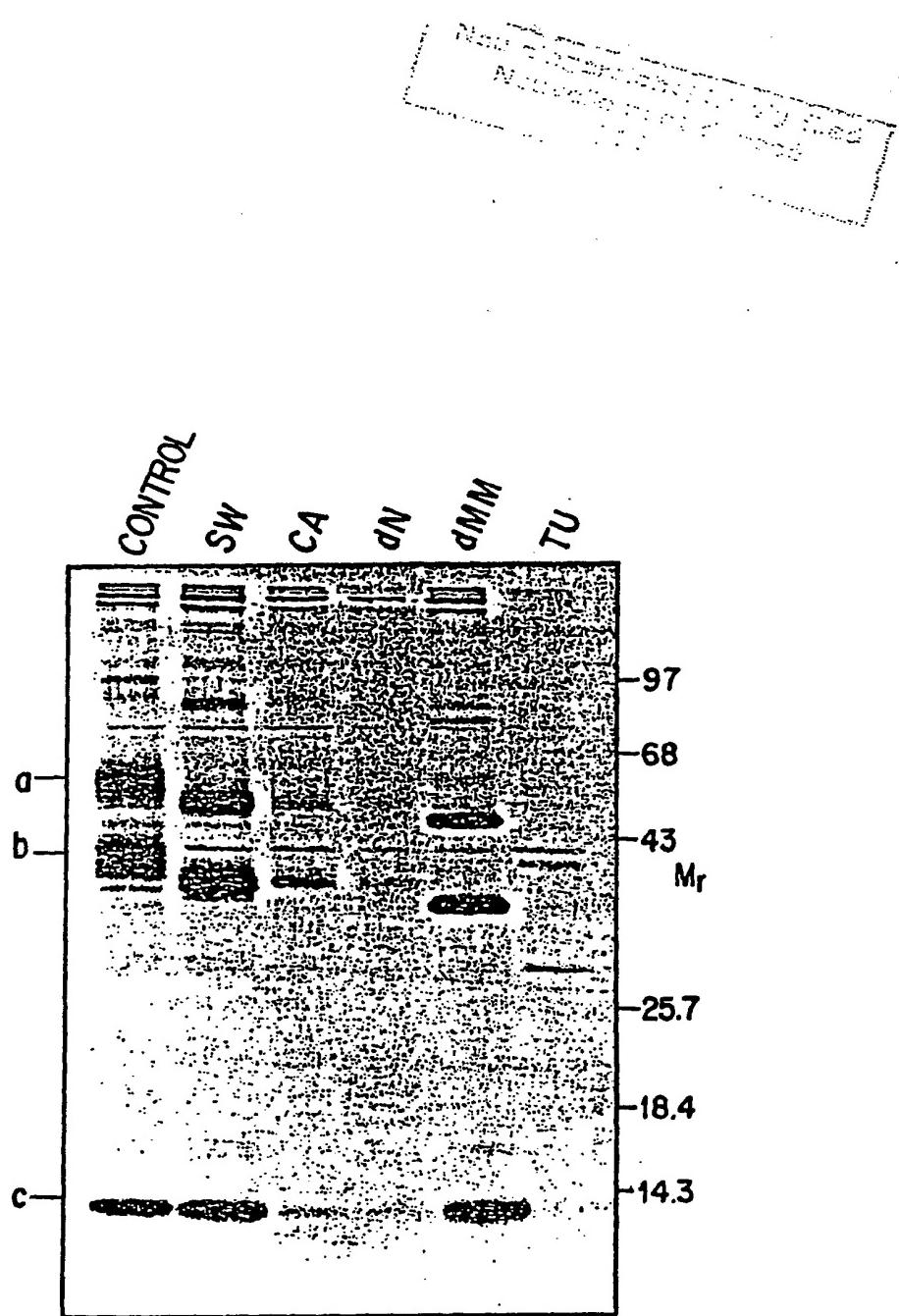


FIG. 43A

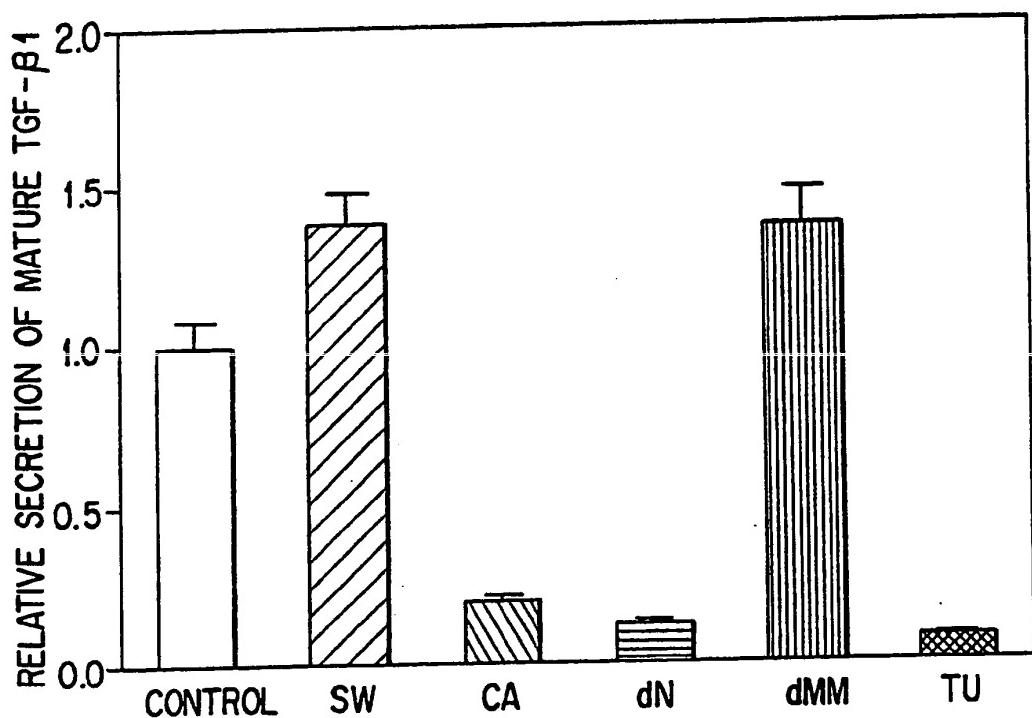


FIG. 43B

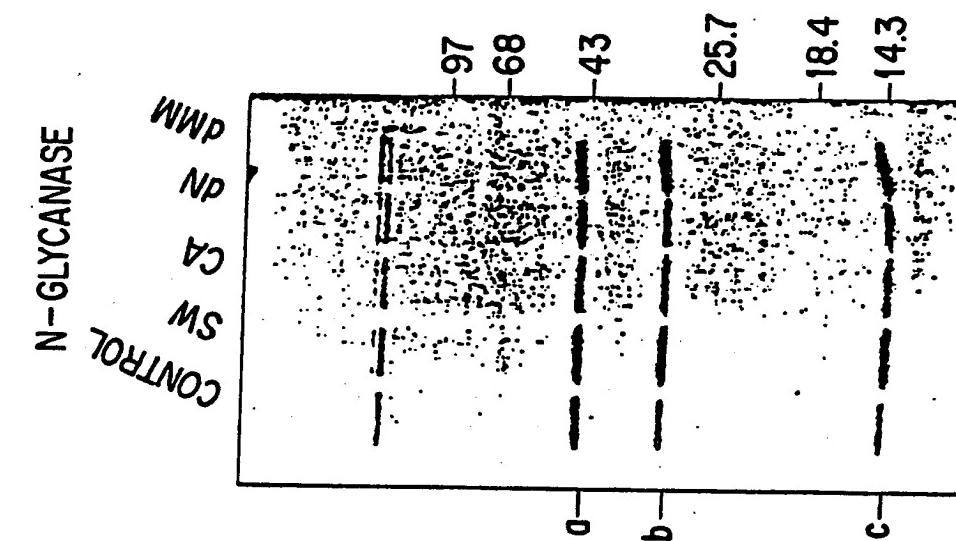


FIG. 44B

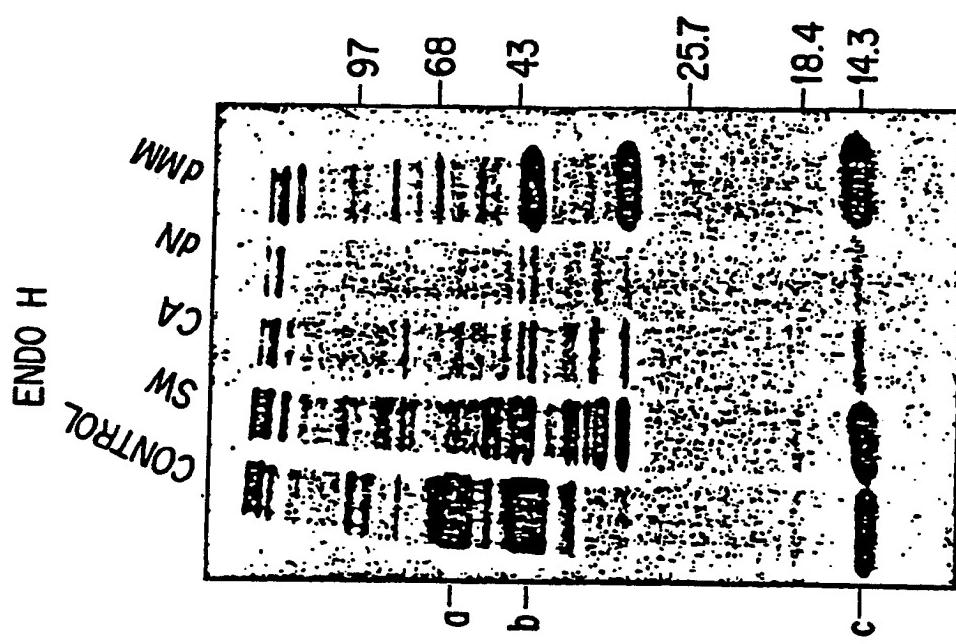


FIG. 44A

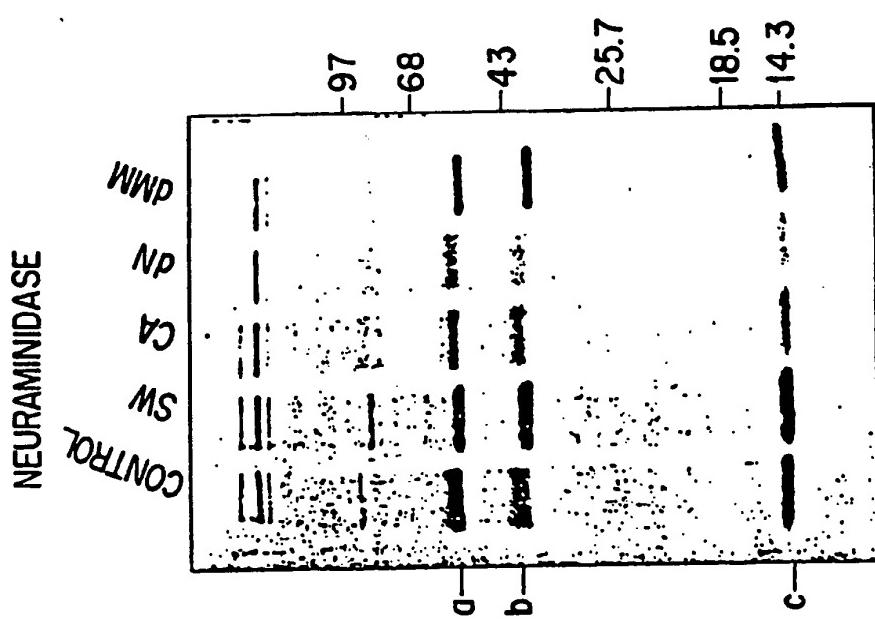
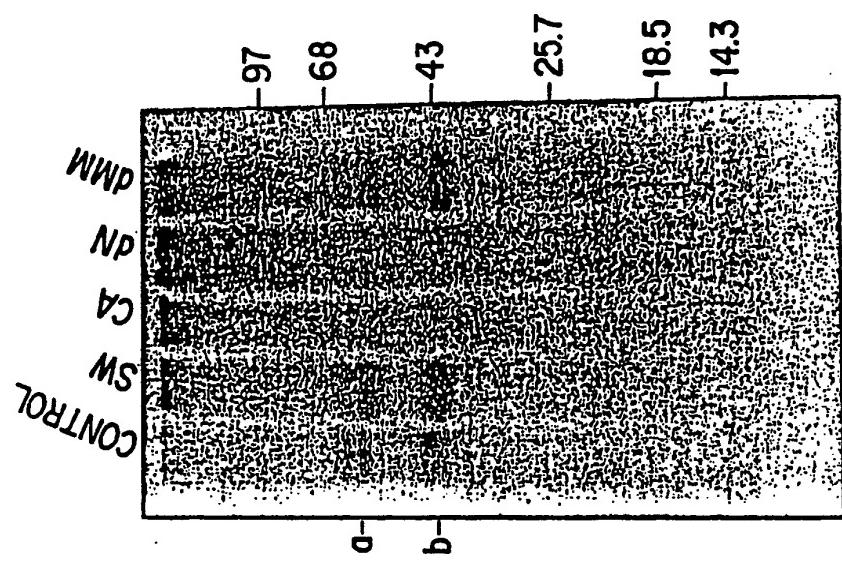


FIG. 45

FIG. 44 C

10.02.9

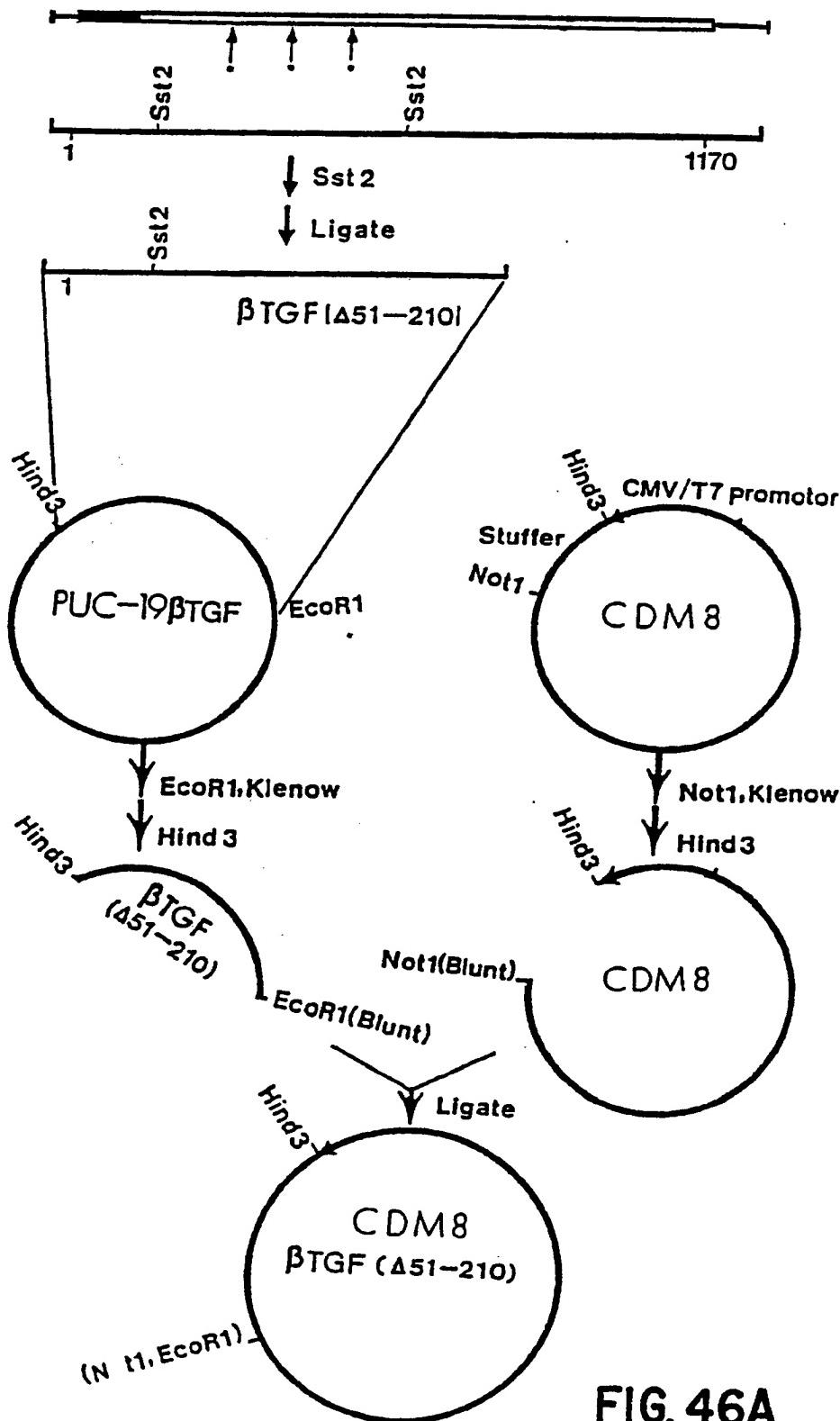


FIG. 46A

1000000

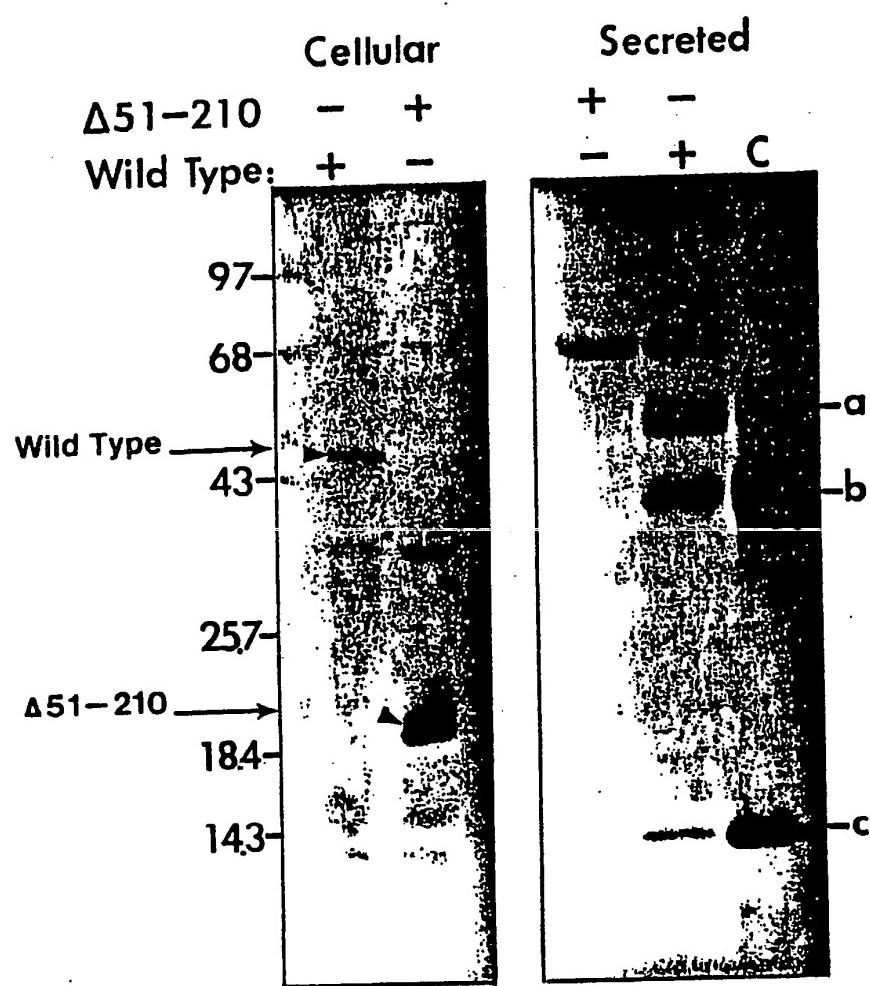


FIG.46 B

10.00.00

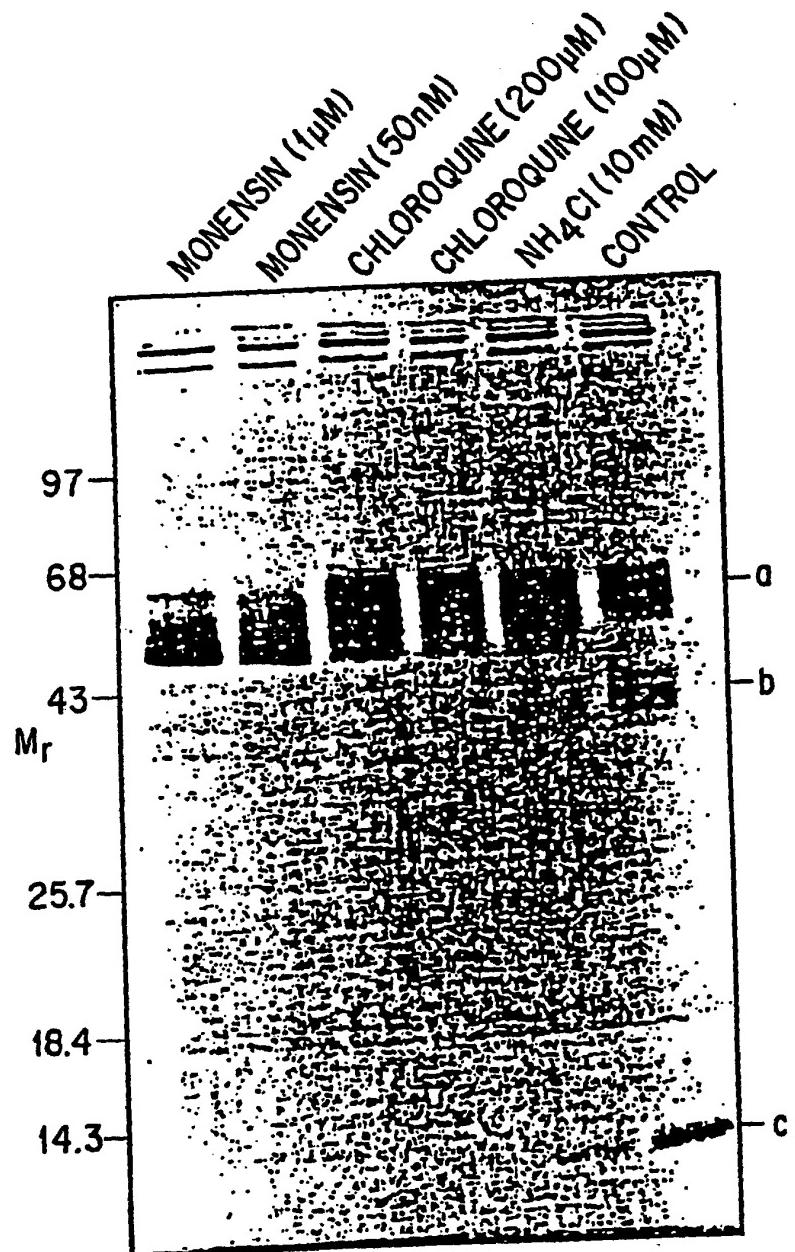


FIG. 47A

10.00.00

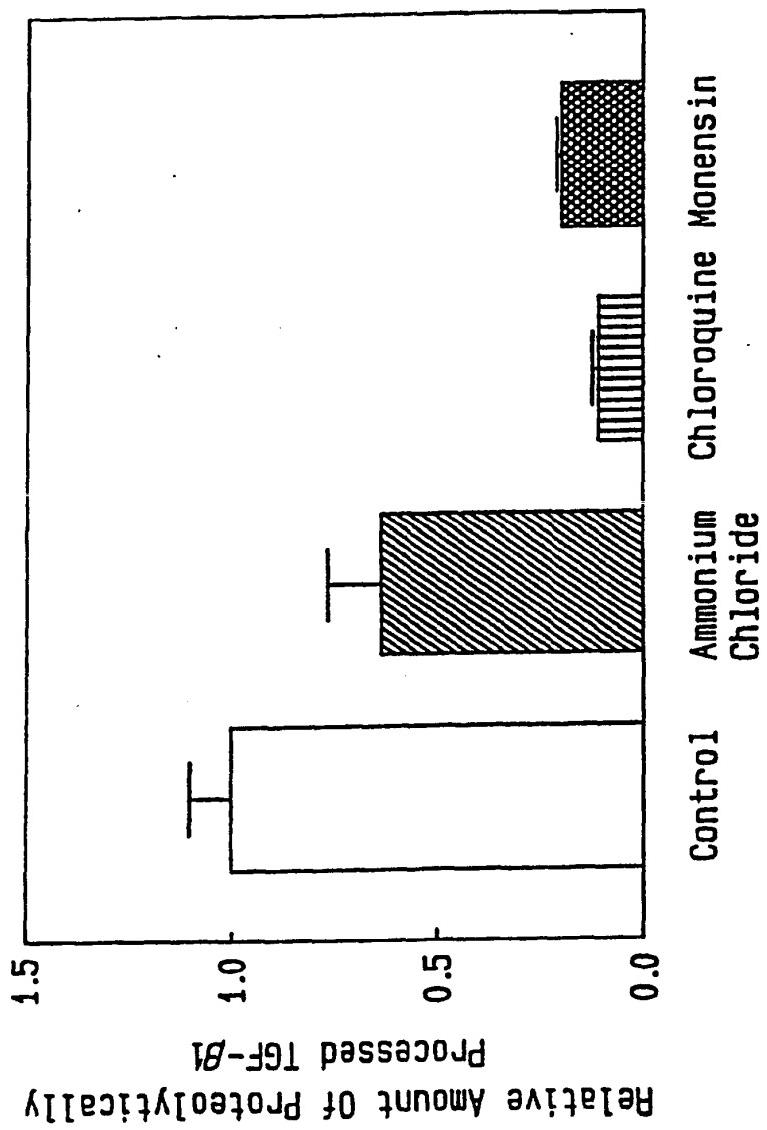
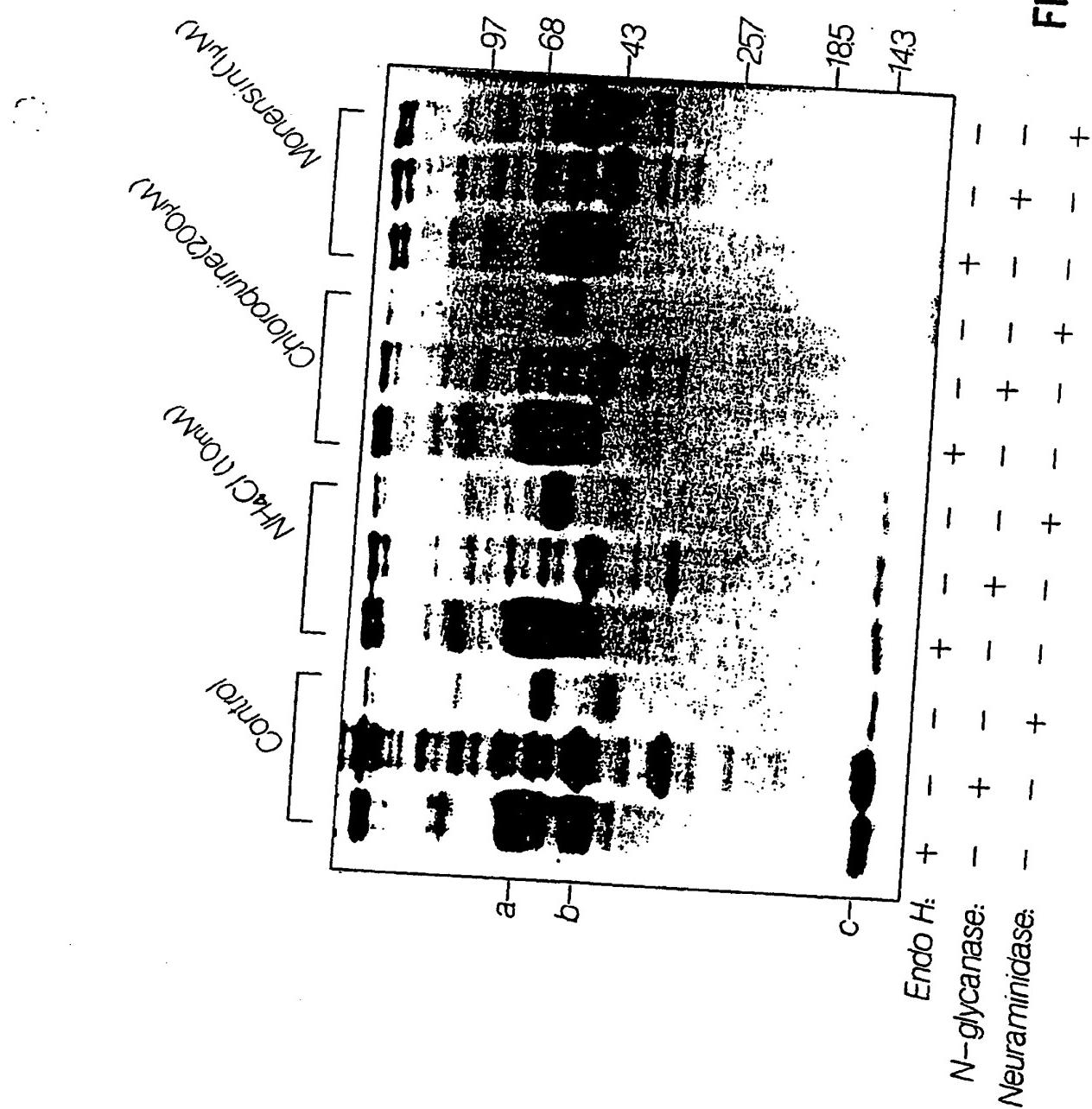


FIG. 47B

FIG. 48



12.10.1990

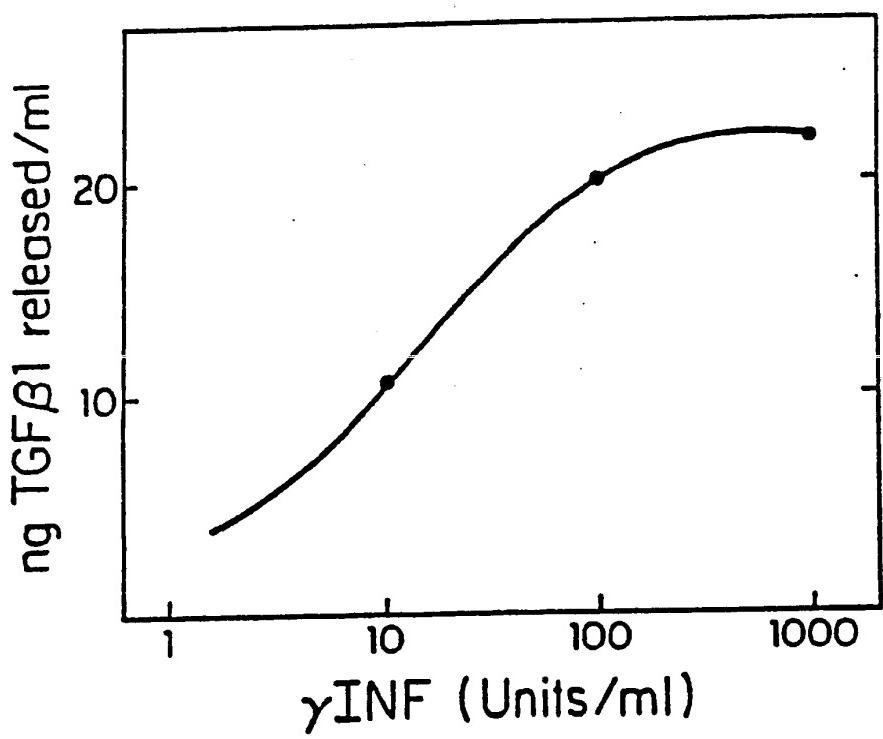


FIG. 49

12.000.00

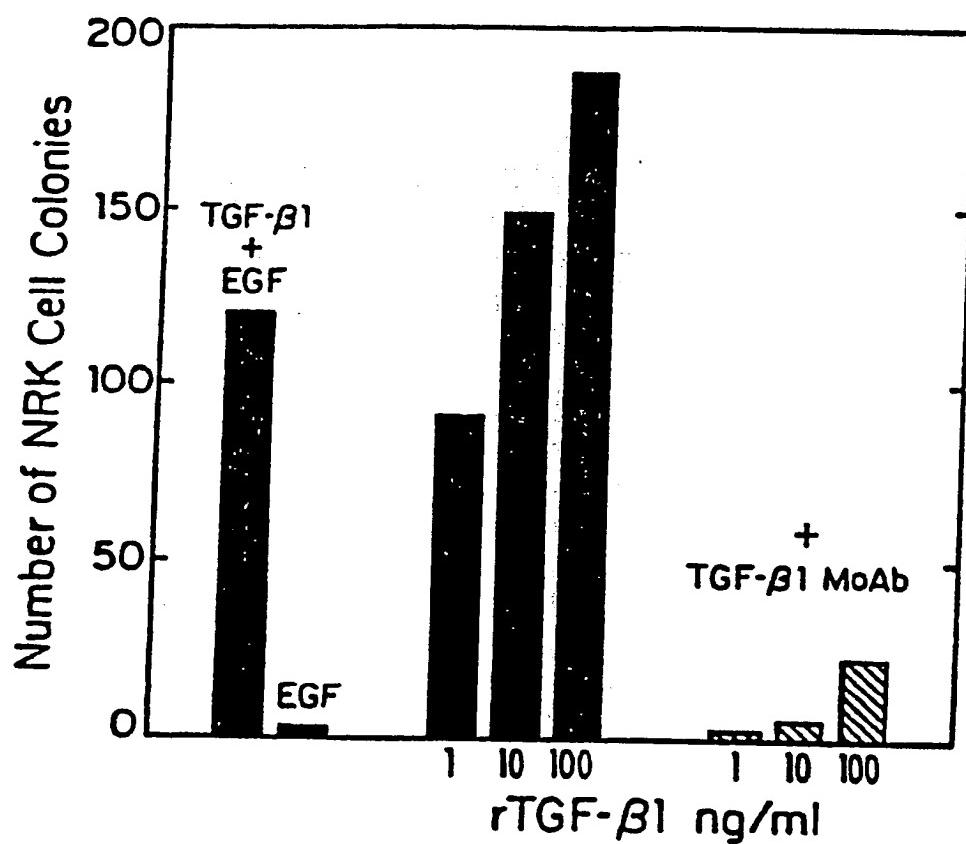
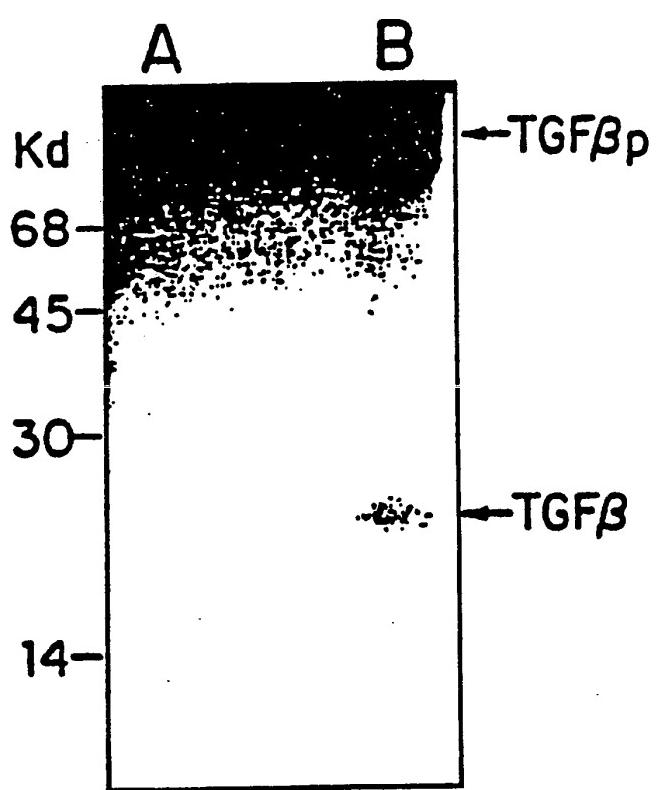


FIG. 50



**FIG. 51**



European Patent  
Office

# EUROPEAN SEARCH REPORT

Application Number

EP 89 40 3294

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 5)
X	EP-A-0 293 785 (ONCOGEN)	1-2, 4- 13, 15- 31, 46, 51 3, 14, 32 -45, 47- 50	C 12 N 15/16 C 12 P 21/02 C 12 N 5/00 C 07 K 13/00 A 61 K 37/02
Y	---	3, 14, 32 -45, 47- 50	
Y	EP-A-0 218 825 (CETUS CORP.) -----		
			TECHNICAL FIELDS SEARCHED (Int. Cl. 5)
			C 12 N C 12 P
The present search report has been drawn up for all claims			
Place of search	Date of completion of the search	Examiner	
THE HAGUE	02-02-1990	VAN PUTTEN A.J.	
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons ..... & : member of the same patent family, corresponding document	

